Remarks:

Please find remarks directed towards the individual points of the examiner's detailed action of the 08/31/2005 office action itemized below:

Objection to the specification:

1.) The examiner objects to new matter added to the specification on page 6, line 16; to page 8, line 10; of the 10 June 2005 amendment. The examiner also objects to what was perceived as new matter contained in pages 17 – 21 of the 10 June 2005 amendment.

The examiner has objected to the addition of entries in the discussion of prior art section. This is the text marked as new (underlined) on page 6, line 16; to page 8, line 10; of the 10 June 2005 amendment. The original submission of this invention did not contain a separate discussion of prior art section. The inventor thought that the placement of a more complete discussion of prior art in its own section, would provide for a more conventional and thorough patent application. The MPEP states that a substitute specification can be submitted in an amendment, as long as its does not add new material to the invention. The inventor presumed this applied only to the details and technical aspects of the invention itself, and not to the discussion of prior art. Thus, the inventor was unaware that the presentation of new material in the discussion of prior art section constituted the addition of new material to the invention. As per the examiner's request, this section has been removed from the application.

The examiner also objects to what was perceived as new matter contained in pages 17 – 21 of the 10 June 2005 amendment.

However, these pages do not contain new matter, but a simple re-statement of the originally submitted brief description of the drawings. In the original specification, the detailed description of the drawings were inadvertently placed in the brief description of the drawings section. This made the detailed description of the invention hard to follow. In the amendment of 10 June 2005, this was corrected by striking out the old brief description of the drawings, and replacing these with one-two sentence entries, which were more appropriate. The detailed text from the original description of the drawings section was then moved en masse into the detailed description of the invention, so that all procedures and references to figures were together. Since large blocks of text were moved from one place to another, the old text was entirely struck out at its old location, and marked as new text in its new location. This text marked as new did not contain new information, it simply marked old text in a new place. The apparent new text on pages 17-21 of the 10 June 2005 amendment are simply the original brief description of the drawings, but in a new place. The text on pages 17-21 of the 10 June 2005 amendment have been re-drafted in the marked-up presentation of the substitute specification presented here, to indicate (by underlining) only areas where new words were added to provide transitions. Thus, it now clearly shows that the text and all technical information was the same as that originally presented

2.) The new material contained in page 6, line 16; to page 8, line 10; of the 10 June 2005 amendment have been canceled. The material contained pages 17 – 21 of the 10 June 2005 amendment have been re-written to indicate that they contain no new matter. A new substitute specification is submitted which is a re-organization of the originally submitted specification, and contains no new matter. The applicant attests that the currently submitted substitute specification contains no new matter.

Further comments on the specification:

The term "sepharose" was incorrectly placed in certain parts of the specification. This was a typographical error. The corrections are noted on pages 24, 33, and 34, of this amendment, where sepharose is struck out and replaced with the correct term sephadex. The functional group, QAE is correct in all cases. Both gels are similar and will perform identically. In order to avoid the use of proper names, the reference to "Bio Rad Multiimager" was eliminated from the specification and replaced by the generic term "CCD camera equipped". Also, the reference to Sigma Chemical was deleted as purified transferrin is available from a wide variety of sources.

Objection to the claims:

1,) The examiner has rejected all claims because they contain matter that was not described in the specification. The term cited in the claims which is in violation is: "human holo-transferrin".

The claims have been re-written to include only terms that were defined in the original specification. The re-drafting of the claims to include only these defined terms produced a marked-up version that was difficult to read, thus all claims are presented as new. The new claims 50 - 55 parallel the previously submitted 43 – 49, in logic and content.

The term "human holo-transferrin" has been replaced with "human iron-saturated transferrin", which is clearly defined in the current and original specification; in line 9 of the detailed description of the invention section.

3.) and 4,) The examiner rejects all pending claims as they fail to particularly point out the invention.

5.) A term which was not adequately defined and is in violation as per 3 and 4 is the term "reaction solution". The reference to this is vague in claim 43. To correct this, this term has been changed to "PB/CHAPS", which is clearly defined in the specification. Claim 43 is replaced with claim 50, and in claim 50 the reference to "PB/CHAPS" in all steps refers to the particular step where "PB/CHAPS" was first defined. To clarify this claim and all others, references to the particular claims and steps where all terms are defined, are included.

6.) The terms "the synthesizing" and "the placing" in claim 43 are not defined, and thus are in violation as per items 3 and 4. To correct this, the word "the" has been omitted from the phrase "the synthesizing". The word "the" was not necessary in this context, in

claim 43, or its replacement: claim 50. The term "the placing" was included in a step describing dialysis in claim 43. As dialysis is a technique widely known to practitioners in the art, this part of the claim has been deleted. The replacement for claim 43: claim 50, contains no such dialysis procedure claim, therefore, the "the placing" statement is no longer present.

6.) The examiner objects to the use of the term "whereby" in clauses at the end of the claims. The examiner recommends the use of the term "wherein" instead. The use of the term "whereby" by the applicant was to add "whereby clauses" to the end of the claims, so as to point out the advantages of the invention or procedure. It is the understanding of the applicant that the term "whereby", serves to add comments to a claim pointing out advantages, whereas the term "wherein" functions to further narrow a claim. The applicant was not desiring to narrow the claims by these comments. Therefore, these components of the claims have been deleted.

Further comments on the claims:

The amended claims further narrow the scope of the claims. The claims objections of the 08/31/2005 OA were relatively minor, but point out a need for more accurately defined and referenced terms throughout. The amended claims now contain only terms which were present in the originally submitted specification. A list of these terms and their origins follows:

The term "Tf" in claim 50 is used as an abbreviation for transferrin. This was defined in the original specification and is located on page 1 of the original specification, and on pages 2 and 21 of the current amendment, in the phrase:

"The major circulating iron transport protein is transferrin (Tf), which exists in"

The terms "buffer" and "PB/CHAPS" in claim 50 are defined on page 11 of the original specification and on pages 6 and 26 of the current amendment, in the sentence:

"Human iron-saturated transferrin was bound to quaternary-amino ethyl (QAE) sephadex in a buffer of 25 mM sodium phosphate, pH 7.2, containing 2 mM of the detergent CHAPS (PB/CHAPS buffer)."

The term "transferrin solution" or "Tf solution" in claim 50 (as Tf had already been defined as transferrin) is defined on page 17 of the original specification and on pages 9 and 32 of the current amendment, in the sentence:

"Iron-saturated human transferrin (Sigma Chemical) was dissolved in PB/CHAPS to a concentration of 10 mg/ml. To 2 ml of Tf solution was added 0.5 ml of equilibrated QAE-sephadex slurry."

The term "EDC-chlorin *e6*" in claim 50 is defined on page 18 of the original specification and on pages 10 and 30 of the current amendment, in the sentence:

"Additional procedure for the preliminary preparation of EDC-chlorin e6:"

The term "QAE-sephadex-Tf" is defined on page 17 of the original specification and on pages 9 and 32 of the current amendment, in the sentence:

"To make the conjugate, to 0.5 ml of QAE-sephadex-Tf was added 0.5 ml of a 2 mg/ml chlorin *e*6 solution."

The term "gel" in claim 50 is referred to numerous times as the matrix to which the quaternary amino ethyl group is attached. Examples are on pages 11 and 17 of the original specification and on pages, 7, 8, 30, and 32 of the current amendment, in the sentences:

"In either case, the transferrin was conjugated while bound to the gel"

"The suspension was centrifuged at 1,000 X g for 5 min and the gel pellet equilibrated"

The use of the term "gel" in reference to certain chromatography materials is common in the art: i.e.: "gel filtration chromatography". Gel is understood by practitioners to refer to various materials, including sephadex and sepharose.

The terms "immobilized transferrin" and "immobilized conjugate" in claim 50 are defined on page 11 of the original specification and on pages 7 and 30 of the current amendment, in the sentence:

"This latter soluble EDC-modified chlorin e6 was added to the immobilized transferrin to produce the immobilized conjugate."

The term "conjugated Tf" (Tf had already been defined as transferrin) is defined on page 18 of the original specification and on pages 9 and 33 of the current amendment, in the sentence:

"To elute the conjugated Tf, the gel was suspended in 1ml PB/CHAPS containing 0.5 M NaCl."

The term "washed" in claim 50 is defined on page 17 of the original specification, and on pages 9 and 33 of the current amendment, in the sentence:

"The gel mixture was rocked again at 25° C for 25 min and the gel was washed four times by repeated suspension in and centrifugation (1,000 X g for 5 min) from 25 ml of PB/CHAPS."

In this context, "gel" and "gel mixture" refer to "conjugated Tf" or "immobilized conjugate", so the terms "washed conjugated Tf" or "washed immobilized conjugate", are defined.

The term "binding to a negatively charged matrix" in claim 52 is referred to on page 18 of the original specification and on pages 11 and 34 of the current amendment, in the sentence:

"Therefore, the transferrin will bind to a negatively charged matrix, and the free chlorin e6 will not."

The term "QAE" is referred to on page 11 of the original specification and on pages 6 and 29 of the current amendment, in the sentence:

"Human iron-saturated transferrin was bound to quaternary-amino ethyl (QAE)..."

Discussion of Prior Art:

The 10 June amendment substitute specification contained a new section on the discussion of prior art. As this was determined to constitute new material, it was removed. In order for the examiner to make use of this discussion, it is included below:

In U.S. patent 4,522,750, a procedure is described for the linking of transferrin to alkaloids. The procedure is similar to this invention, except that the transferrin is not immobilized first. The conjugate is an alkaloid and not a photodynamic agent. The compounds were tested for their ability to decrease leukemia growth in mice, where an effect was seen. However, no mention of the actual testing of the conjugates in regards to their acting through a bona fide transferrin/transferrin receptor mechanism is mentioned.

In U.S. patent 4,590,001 the binding of platinum to transferrin for use as an anti-cancer agent is described. The binding procedure and the toxic compound are different than the ones mentioned in this application.

In U.S. patent 5,876,989, the use of a three component system for delivering photosensitizers into cells is mentioned. This consists of a photodynamic therapy agent, a molecule of interest, and a carrier molecule. The molecule of interest could be transferrin. The photodynamic therapy agent could be a chlorin. The showing of a forming of a conjugate of these is not made: they are administered together, but not as a linked conjugate.

In U.S. patent 5,906,977, the use of an inflammatory disease treating complex consisting of an active substance, a linker, and a carrier is discussed. The active substance could be a photodynamically active compound. The carrier could be transferrin. The method of conjugate synthesis is different than that here. The display of

a biologically active transferrin conjugate is not shown. The use as an anti cancer agent is not discussed.

In U.S. patent 6,500,800, the use of a five component complex for causing damage to cells by photodynamic therapy is shown. The conjugates differ from the one here since in the current application, the carrier protein is missing. Also, the method of conjugation is different. Transferrin is mentioned as being a potential ligand, but the actual synthesis and testing of a transferrin-based conjugate is not shown.

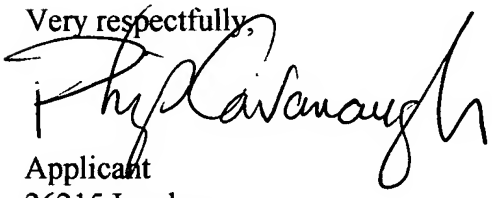
In U.S. Patent 6,610,298, the use of photodynamic agent conjugates for treating mycobacterial infections is shown. The conjugates consist of a photosensitizer and a liposomal targeting moiety. The photosensitizer could be a chlorin. The targeting moiety could be transferrin. The conjugation method used does not involve immobilization of the protein prior to conjugation. The actual use of a transferrin conjugate is not presented. The use of these conjugates as an anti cancer agent is not discussed.

U.S. Patent 6,812,209 is for conjugates of active compounds with native proteins. The active compound could be a photodynamic agent. The possibility that the protein could be transferrin is mentioned in the detailed description. The conjugation method used does not involve immobilization of the protein prior to conjugation. This invention covers a whole host of protein-based therapeutic reagents wherein the protein is conjugated with a chemotherapeutic or photodynamic agent. However, the specific protein mentioned in the claims is albumin.

Request for constructive assistance

The applicant has amended the specification, and claims so that they are proper and define a novel non-obvious method. If this application is not believed to be in condition for allowance, the applicant respectfully requests the constructive assistance and suggestions of the examiner pursuant to MPEP 2173.02 and 707.07(j), in order so that the applicant can submit an allowable application as soon as possible.

Very respectfully,



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